REMARKS

Applicants respectfully request reconsideration of the captioned application in light of the attached 132 Declaration and the below remarks.

Claim Rejections Under 35 U.S.C. § 103

Claims 1-2, 5-7, 9-10, 13-17, 28, 71, and 80 stand rejected under 35 U.S.C. § 103(a) for allegedly being obvious over Ebert *et al.*, European Journal of Pharmacology, Aug. 20, 1997, 333 (1):99-104, ("Ebert") in view of US Patent Application 2005/0148673 ("Harbut"). This rejection is respectfully traversed for the reasons provided below.

The Examiner has contended that it would have been *prima facie* obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to have substituted substantially enantiomerically pure (S)-norketamine as disclosed by Ebert for the ketamine in the method of treating neuropathic pain as disclosed by Harbut, Page 4 of the Office Action dated 15 April 2008. In the previous paragraph of the same Office Action, the Examiner had stated that (S)–norketamine contributed significantly to the clinical activity of (S) ketamine, and that following oral administration of (RS)-ketamine, (S)–norketamine will be present in human plasma at sufficiently high concentrations to account for some of the observed analgesic activity.

The Attached 132 Declaration by Dr. Kleven Demonstrates Unexpected Results, Which Overcome the Examiner's Section 103 Rejections

In the concurrently filed 132 Declaration by Dr. Mark Kleven, a PhD pharmacologist with decades of academic and industry experience, *in vivo* data are presented showing that (S)-norketamine, given at an e*quipotent dosage*, results in an unexpected reduction of side effects in comparison to an equipotent dosabe of racemic ketamine. See Kleven Declaration, p. 3, item 7.

As shown in Figure 1 and described in Item 9, page 4 of the Kleven Declaration, a rat chronic construction injury (CCI) model was used to determine that a 1 mg/kg dosage of S(+)-norketamine was equipotent to 8 mg/kg of (±)-ketamine. That is, both of these amounts achieved a maximum possible effect against mechanical hyperalgesia, i.e., an increased

response to pain, indicative of increased sensitivity to pain. As noted by Dr. Kleven, the equipotent amounts achieved a maximum possible effect against mechanical hyperalgesia, *and therefore having an equivalent therapeutic effect, would be expected to produce equivalent side effects*. *Id.* p. 4, item 9.

Unexpectedly, however, although S(+)-norketamine was given at an equipotent dose to (±)-ketamine, less ataxia and stereotypic behaviors were displayed by the rats in the *in vivo* model. "Both S(+)- and R(-)-norketamine (IP) produced significantly less ataxia and stereotypic behaviors compared to (±)-ketamine at doses maximally effective against mechanical hyperalgesia." *Id.* p. 5, item 11. As defined in Table 1 at page 7 of the Kleven Declaration, ataxia ranges from jerky movement and loss of balance to being unable to walk. Stereotypic behaviors worsen from head bobbing, to head swinging, to shaking, twitching and weaving. As stated by Dr. Kleven in the Declaration at page 5, item 11 and shown in Figure 2A, "S(+)-norketamine produced 5.0 fold less ataxia, although it would have been expected to be equal to ketamine." *Id.* p. 5, item 11.

Also, racemic ketamine was observed to evoke a PCP-like behavior within five minutes, but this effect was not observed with S(+)-norketamine at any dosage tested. *Id.* p. 5, item 11. A PCP-like behavior in an animal model is predictive of PCP like behaviors in humans. PCP or phenylcyclohexylpiperidine, abbreviated as phencyclidine, is an NMDA receptor antagonist and a powerful hallucinogen, sold illegally with the street name "angel dust." See Harbut, paragraph no. [0031]. Users experience vivid hallucinations, and can turn violent and psychotic. *Id.* PCP is considered one of the most dangerous of all recreational drugs. *Id.*

Applicants submit that the Kleven Declaration evidences an unexpected beneficial result not taught or suggested by Ebert or Harbut, either alone or in any combination. Based on the teachings of Ebert and Harbut, one of skill in the art could not have reasonably expected that administration of (S)-norketamine, at an equipotent amount to racemic ketamine (i.e., double the amount of (RS)-ketamine), would have resulted in significantly less *in vivo* side effects in comparison to racemic ketamine. Therefore, based on the evidence of the Kleven Declaration, applicants request that the rejection for alleged obviousness be withdrawn and the application be placed in condition for allowance.

Applicants also attach hereto, as Exhibit 1, an Article in Press, for Pharmacology, Biochemistry and Behavior co-authored, *inter alia*, by Peter Crooks, one of inventors and Dr. Kleven. Exhibit 1 discusses the data presented in the Kleven Declaration.

The Examiner Has Not Established a Prima Facie Case of Obviousness

Harbut Does Not Provide Motivation or a Reasonable Expectation of Success and is A Teaching Away

Applicants contend that when the teachings of Harbut, as they relate to norketamine, are viewed as a whole, Harbut would not have provided either motivation to combine with Ebert or a reasonable expectation of success. Norketamine is mentioned only four times by Harbut, in paragraph nos. [0081], [0113] and [0136]. The sentences mentioning norketamine are reproduced below.

> Intravenous infusion is regarded as the preferable mode of administration, since (i) it can avoid the types of adverse skin-related side effects that were reported in Eide et al 1995, and (ii) it can also maximize the effects that can be exerted by the ketamine before it is metabolically degraded into metabolites such as norketamine, which is only about 25% as effective as ketamine in reducing pain signals. (Paragraph no. [0081]).
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> Prolonged subcutaneous infusions of ketamine were tested in the mid-1990's, as reported in Eide et al 1995[1], summarized above; however, subcutaneous infusions must be infused so slowly that much of the ketamine is likely to be metabolized to norketamine before it can exert its effects, and Eide et al reported that their treatment was "associated with intolerable side effects" (quoted from their abstract). (Paragraph no. [0113]).
>
> Blood from one patient was analyzed for norketamine, a metabolite of ketamine that is only about 25% as effective as ketamine in suppressing activity at NMDA receptors. That analysis indicated a high level of norketamine, which confirmed that certain enzymes in that patient were unusually active in rapidly degrading ketamine. (Paragraph no. [0136]).

In Harbut, norketamine is disclosed as a metabolite of ketamine, which is only about 25% as effective as ketamine in suppressing activity at NMDA receptors. When discussing a study involving prolonged subcutaneous infusions of ketamine, Harbut notes that a disadvantage to this mode of administration is that infusion occurs "so slowly that much of

[1] Both of the Eide et al. references cited by Harbut are presented in the concurrently filed IDS.

the ketamine is likely to be metabolized to norketamine before it can exert its effects," and that this treatment was "associated with intolerable side effects."

When read in its totality, Harbut portrays norketamine in a negative light when compared to ketamine. Norketamine is taught to be less effective than ketamine in suppressing activity at NMDA receptors. Ketamine should be administered sufficiently fast to avoid its apparently undesirable metabolism into norketamine. A treatment that likely resulted in high metabolic levels of norketamine was also associated with intolerable side effects. These statements amount to Harbut teaching away from the use of norketamine, rather than being suggestive of using norketamine.

Therefore, when the teachings of Harbut are viewed in their context, one of skill in the art would not have been motivated to combine Harbut with Ebert and practice a therapy involving norketamine, and, in addition, one of ordinary skill would not have had a reasonable expectation of success. Instead, Harbut would have been viewed as a teaching away from the use of norketamine.

Not All of the Claimed Elements are Taught or Suggested by the Prior Art

All of the independent claims of the captioned application recite that the amount of norketamine is "effective to treat pain while not inducing dysphoria." Additionally, independent claims 1 and 16 recite that the administered range is about "about 0.01 to about 20 mg/kg of body weight of the patient." Applicants contend that this dosage amount is not suggested in either Ebert or Harbut for norketamine.

Furthermore, the Examiner citing *In re Spada* as support, argues that the recited dosage amounts are inherently below a level to induce dysphoria since a composition and its properties are inseparable. See Office Action dated April 15, 2008. Applicants respectfully submit that *In re Spada* does not support the Examiner's inherency argument with respect to the examined claims, because these are method of treatment claims and the holding of *In re Spada* was related to composition claims, not method of treatment. Specifically, the Federal Circuit held that "when claimed compositions are not novel they are not rendered patentable by recitation of properties, whether or not these properties are shown or suggested in the prior

art." In *Re Spada*, 911 F.2d. 705, 709 (CAFC 1990). Thus, reliance on *In re Spada* is not warranted.

Therefore, applicants contend that the combination of Ebert and Harbut does not give rise to a finding of *prima facie* obviousness. Moreover, even if the Examiner believes a *prima facie* case of obviousness has been established, applicants urge that the unexpected results of the data presented in the Kleven Declaration overcome the *prima facie* case of obviousness and place the application in condition for allowance.

Conclusion

Applicants respectfully submit that the present set of claims satisfies all statutory requirements and recites subject matter that is patentable over the disclosures of the prior art of record. A Notice of Allowance is cordially solicited.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,
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